

- E1
- 4 (i) transforming a mouse ES cell with a first DNA construct encoding  
5 a first indicator component under the control of a promoter having restricted expression  
6 in a mouse;  
7 (ii) transforming the cell of (i) or a descendent of the cell by operably  
8 integrating into the cell's genome, a second DNA construct comprising DNA encoding a  
9 second indicator component not operably linked to a transcription control element;  
10 (iii) producing tissue or specialized cells from the cell of (ii); and  
11 (iv) monitoring the tissue or specialized cells of (iii) for a detectable  
12 indicator resulting from both the first and second indicator components indicative of  
13 integration of the second DNA construct into a gene having restricted expression.

- E2
- 1 ~~5~~ ~~6~~ (Twice Amended) The method of claim 1 which additionally  
2 comprises isolating DNA endogenous to the mouse ES cell or descendent thereof which  
3 flanks the second DNA construct integrated into a gene having restricted expression.

- ~~E3~~  
SUB  
F1
- 1 12. (Twice Amended) The combination of:  
2 (i) a DNA construct for integration into the genome of an eukaryotic cell  
3 comprising a sequence encoding a first indicator component under the control of a  
4 promoter having restricted expression; and  
5 (ii) a DNA construct for integration into the genome of a eukaryotic cell,  
6 comprising in the 5' to 3' direction, a splice acceptor, a sequence encoding a second  
7 indicator component not operably linked to a transcription control element, and an  
8 optional IRES, wherein expression of both the first and second indicator components in  
9 said cell is detectable, and wherein in the absence of either indicator component, there is  
10 no detectable indicator.

- E4
- 1 ~~3~~ ~~13~~. (Twice Amended) A mouse ES cell or descendent thereof,  
2 transformed by the combination of DNA constructs of claim ~~12~~ <sup>1</sup>.

1 ~~12~~ 18. (Twice Amended) A method of producing mouse tissue or  
2 specialized cells comprising a detectable indicator associated with a target gene having  
3 restricted expression, which comprises:  
4 (i) transforming a mouse ES cell with a first DNA construct encoding  
5 a first indicator component under the control of a promoter having restricted expression  
6 in a mouse;  
7 (ii) transforming the cell of (i) or a descendent of the cell by  
8 integrating into the cell's genome, a second DNA construct comprising DNA encoding a  
9 second indicator component not operably linked to a transcription control element;  
10 (iii) producing tissue or specialized cells from the cell of (ii); and  
11 (iv) selecting tissue or specialized cells of (iii) by the presence of a  
12 detectable indicator resulting from both the first and second indicator components.

1 ~~13~~ 19. (Twice Amended) A method of producing a mouse comprising a  
2 detectable indicator associated with a target gene having restricted expression, which  
3 comprises:  
4 (i) transforming a mouse ES cell by integrating into the cell's genome,  
5 a first DNA construct encoding a first indicator component under the control of a  
6 promoter having restricted expression;  
7 (ii) transforming the cell of (i) or a descendent of the cell by  
8 integrating into the cell's genome, a second DNA construct comprising DNA encoding a  
9 second indicator component not operably linked to a transcription control element;  
10 (iii) selecting transformed cells of (ii);  
11 (iv) introducing selected cells of (iii) into a mouse host embryo;  
12 (v) implanting the host embryo of (iv) into a pseudopregnant mouse;  
13 (vi) maintaining the mouse of (v) while offspring develops to term  
14 from the host embryo; and